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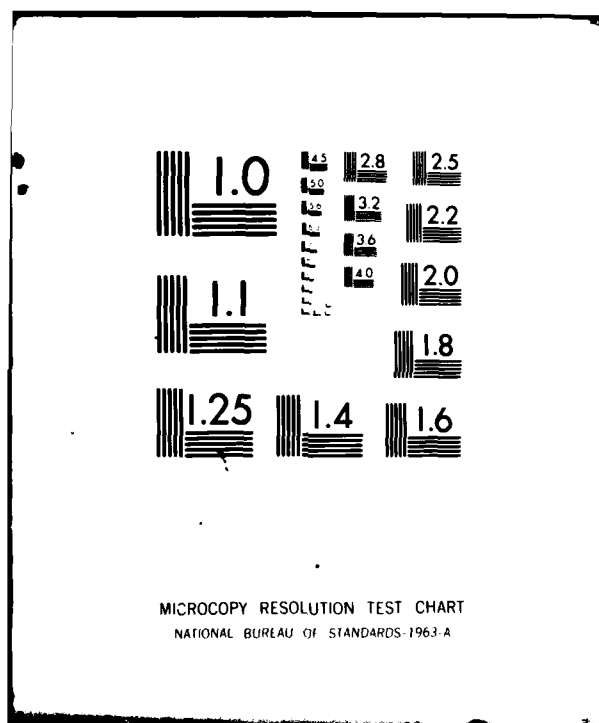
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TAMING EFFECTS OF p-CHLOROPHENYLALANINE
ON THE AGGRESSIVE BEHAVIOR OF SEPTAL RATS^{1,2}

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JONES, ALAN B., BARCHAS, JACK D. AND BURR EICHELMAN. *Taming effects of p-chlorophenylalanine on the aggressive behavior of septal rats.*

PHYSIOL. BEHAV. Septal irritability and shock-induced aggression were suppressed by the administration of p-chlorophenylalanine to septal rats. Septal irritability was more effectively reduced than shock-induced aggression, but both the levels of septal irritability and shock-induced fighting were significantly lower than in nontreated septal rats. Since both parameters of septal aggression were reduced by PCPA, and while PCPA has no effect on shock-induced fighting of unlesioned rats, it appears that both forms of aggression may function through a common neural mechanism.

Septum

Irritability

Fighting

Septal syndrome

PCPA

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Lesions in the septal area of the rat brain produce a septal rage syndrome characterized by excessive irritability, hyperactivity and increased aggressiveness [1, 3, 5, 9, 13, 20]. Septal lesions increase generalized irritability [5], sensitivity to pain [9,16], and shock-induced aggression [1, 4, 9, 22]. This syndrome declines markedly within two to three weeks following surgery [5].

Septal irritability is rapidly suppressed by ip injections of parachlorophenylalanine (PCPA) [7] within 30 minutes [8]. PCPA does not affect the levels of shock-induced aggression in unlesioned rats [6, 11]. Consequently this study was designed to test whether a PCPA-induced attenuation of septal irritability also lowered the level of shock-induced aggression observed in rats with septal lesions, which would suggest that both types of aggression might be of common etiology.

METHOD

Animals

The subjects were 54 naive male albino rats (Sprague-Dawley) from Simonsen Laboratories of Gilroy, California, weighing from 180-200 g at arrival. All animals were housed individually with ad-lib access to rat chow and water throughout the experiment.

Apparatus

The testing chambers for shock-induced fighting consisted of two 32 x 25.5 x 30.5 cm blue Plexiglas boxes, each with one clear side for viewing. The grid floors were made of stainless-steel rods, 0.3 cm in diameter and spaced 1.9 cm apart. Electric shock was delivered by a

power source adapted from Belluzzi and Grossman [2]. All footshock was of 2 ma intensity, presented for a duration of 0.4 sec and delivered by a cycling timer every 7.5 sec. During each daily test session each rat pair received 50 footshocks.

Behavioral Paradigms

Irritability was evaluated using the rating-scale developed by Brady and Nauta [5]. Ratings were made of all animals for the following seven behavior components: (a) resistance to capture in the home cage, (b) resistance to handling, (c) muscular tension elicited in reaction to capture and handling, (d) squealing and vocalization elicited by reaction to capture and handling, (e) urination and/or defecation elicited by capture and handling, (f) aggressive reaction elicited by the presentation of forceps in close proximity to the snout, and (g) aggressive reaction elicited by prodding with forceps.

A four-point rating scale was used for each of the seven behavior components. The zero point was fixed by the behavior of tame albino rats such as those conventionally employed in laboratory experiments. Ratings of all animals were made on the three days prior to the operation and for the six consecutive postoperative days.

During shock-induced fighting, an aggressive attack was defined as a directed movement toward the opponent which resulted in contact, including at least one additional response of the following: biting, sparring, upright attack posturing, or supine submissive posturing, adopted by the attacked rat. For each day, an attack/shock percentage was calculated (the number of attacks divided by the number of shocks administered X 100). This daily percentage was then averaged over the

test days to provide preoperative and postoperative mean levels of fighting.

Surgery

At the time of surgery, all rats were injected ip with 7.5 mg of atropine methyl nitrate to reduce secretions in airways. This was given 10-15 minutes before pentobarbital (60 mg/kg, ip). Occasionally the pentobarbital was supplemented briefly with ether during the operative procedure. Lesions were made in the usual stereotaxic manner using cathodal current passed through an insulated stainless-steel electrode. The anode was placed in the rat's rectum. Following the lesion, the burr holes were covered with Gelfoam and the incision closed with wound clips. Postoperatively each animal received one im injection of 75,000 units of penicillin.

The lesions were made according to coordinates taken from Pellegrino and Cushman [18]. One bilateral placement was used at current parameters of 3 ma for 45 sec. Controls received the identical operative procedure but without the disruption of the dura or the insertion of an electrode.

Histology

Upon completion of the study, the subjects were perfused by cardiac puncture with 50 cc of normal saline, followed by 50 cc of 10% Formalin. The brains were blocked, embedded in paraffin, and sectioned at 6-8 μ . Every tenth section through the lesion was mounted and stained with cresyl violet.

Procedure

On preoperative days one through three, each animal was removed from its cage and an irritability rating assessed after Brady and Nauta [5], from 8:00 to 10:00 a.m. The rats were then paired and tested for shock-induced aggression in pairs which remained constant throughout the experiment.

On postoperative days one through six, each animal was again removed from its cage between 8:00 and 10:00 a.m., an irritability rating was assessed, and an ip injection of either 0.9% saline or 300 mg/kg of PCPA methyl ester suspended in 0.9% saline was administered. Eighteen rats which received septal lesions were given PCPA (S-PCPA), eighteen rats which received septal lesions were given saline (S), and eighteen control rats received sham operations and were given saline (C). Four hours after the injection, each animal was removed from its cage, an irritability rating was again determined, and the rats were tested for shock-induced aggression. Each pair of rats received a total of 50 footshocks daily.

RESULTS

Histology

The septal lesions damaged large areas of the lateral and medial septal nuclei. They interrupted the precommissural fornix, the hippocampal commissure, and the descending columns of the fornix. They consistently damaged portions of the anterior commissure, the nucleus proprius of both the anterior commissure and the stria terminalis, the medial parolfactory nuclei, and the diagonal band of Broca. Less

consistent damage occurred to the nuclei accumbens septi and the paraventricular hypothalamic nucleus. A number of lesions damaged ventral medial portions of the corpus callosum. An illustrative lesion is shown in Figure 1.

Irritability ratings. Table 1 presents the mean changes in irritability from preoperative baselines for the first three days postoperatively and the first six days postoperatively. During the first three days postoperatively both the septal ($p < .001$) and the septal-PCPA ($p < .001$) groups were significantly more irritable. For the six day mean, however, only the septal group was significantly more irritable than its preoperative baseline level ($p < .001$). The sham group showed no significant increase in irritability.

All three groups were significantly different from one another, although for both three-day and six-day means the sham group differed from the septal-PCPA group on one-tailed t-test only ($p < .05$). Sham versus septal and septal versus septal-PCPA comparisons differed at a higher level of significance ($p < .001$, 2-tailed).

Shock-induced aggression. Table 2 presents the mean changes in the incidence of shock-elicited fighting between a three-day baseline and three-day or six-day postoperative mean levels. The control group (sham-operated) showed a significant ($p < .001$) decrease in shock-induced fighting (characteristic of certain strains [10]) over the first three postoperative days; this decrease was no longer significant in the six-day postoperative comparison. The septal lesion group, conversely, demonstrated a significant increase ($p < .05$). The septal-PCPA group was intermediate and did not differ from baseline levels of shock-induced aggression.

All three groups differed from one another on one-tailed t-test. The sham group was slightly less aggressive than the septal-PCPA group ($p < .05$, one-tailed) three days postoperatively, but this difference was no longer significant over the six-day postoperative period. The sham group versus the septal group and the septal-PCPA group versus the septal group both exhibited significant differences in levels of shock-induced fighting ($p < .01$), the septal group being more aggressive than either the sham or septal-PCPA group.

DISCUSSION

These experiments confirm the previous reports [3, 5, 19] that septal lesions induce hyperirritability and increase shock-induced aggression in the rat [1, 4, 9, 22]. PCPA significantly suppressed not only the hyperirritability as indicated by other experiments [7, 8], but also suppressed the increase in attacks during shock-induced fighting.

The simplest explanation of these data is that the increase in attacks during shock-induced aggression is concomitant with the hyperirritability exhibited in the septal syndrome, both aspects of which may be conjointly suppressed with PCPA. This is supported by the finding that PCPA administered to normal rats has no effect on the level of shock-induced aggression [6, 11]. This explanation is further corroborated by the observation that as the septal syndrome attenuates over time, the increase in shock-induced fighting also diminishes toward control levels [1]. A similar parallel appears to exist with muricidal behavior induced by septal lesions in rats, since there is an increase in the mouse killing behavior up to 10 days after lesioning [21] but not after 15 days [12, 17]. This data also implies a strong correlation of

predatory aggression with the duration of the septal syndrome. These data appear to support the contention that various categories of aggression elicited by septal lesions on the rat are related by a common neural mechanism.

The serotonin-depleting effect of PCPA, a tryptophan hydroxylase inhibitor [15], may not be the direct mechanism for the behavioral effects reported above, since this action of PCPA requires several hours to days to produce a measurable change. The rapidity of onset of the behavioral effects (30 min, [8]) suggests changes which might be occurring at the synapse and nerve terminal. One possible mechanism is suggested by Knapp and Mandell [14] who have shown that PCPA decreases the synaptic uptake of tryptophan, a serotonin precursor. If PCPA also interferes with the reuptake of serotonin, it may initially leave more functional serotonin available. This could conceivably compensate for the damage to serotonergic terminals in the septum and aid in a restoration of more normal behavior. Such a hypothesis implicates a septal-serotonergic system which when functional, inhibits several forms of rodent aggression.

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FOOTNOTES

1. This research was supported by Grant #NR 101-715 from Office of Naval Research. JDB holds Research Scientist Development Award MH 24,161.
2. The research reported here was submitted to Stanford University in partial fulfillment of the M.A. degree.
3. Reprint requests should be addressed to B. Eichelman.

FIGURE LEGEND

Figure 1. Photomicrograph demonstrating representative septal damage.

TABLE 1.

Mean differences in irritability ratings for each group for three-day preoperative averages versus both three-day postoperative and six-day postoperative averages.

Group (N)	Prelesion	Postlesion 3 Days	Δ	Postlesion 6 Days	Δ
Sham (18)	.98	1.63	+1.65*	1.32	+.34
Septal-PCPA (18)	1.65	3.32	+1.67**	1.47	-.20
Septal (18)	.98	8.46	+7.48**	5.55	+4.57**

Note - Probabilities for matched pairs t-test, two-tailed.

* $p < .05$

** $p < .001$

TABLE 2.

Mean differences in shock-induced attack scores following lesions.

Group (N)	Prelesion		Postlesion 3 Days		Difference in % Attacks	Postlesion 6 Days		Difference in % Attacks
	Attacks per 50 Shocks	%	Attacks per 50 Shocks	%		Attacks per 50 Shocks	%	
Sham (9)	24.2	48.2	17.3	34.6	-13.5**	20.9	41.8	-6.4
Septal-PCPA (9)	22.8	45.6	21.3	42.5	- 3.1	21.1	42.1	-3.5
Septal (9)	14.5	29.0	23.2	46.4	+17.4*	24.2	48.5	+19.5*

Note - Probabilities for matched pairs t-test, two-tailed.

* $p < .05$ ** $p < .001$

